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EXAMINER	
ZISKA, S	

ART UNIT	PAPER NUMBER
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DATE MAILED: 06/23/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8/27/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), zero (0) days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1 - 11 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-11 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

This application should be reviewed for errors.

Claims 1-11 are examined in this Office Action.

35 U.S.C. 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34-39, 68, 69 and 82 of copending application serial no. 08/031,801. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the claims embrace each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29, 30 and 33-35 of copending application serial no. 07/919,297. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the claims embrace each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance

with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description of the invention and for failing to adequately teach how to make and/or use the invention as claimed, i.e., failing to provide an enabling disclosure. Applicants have disclosed use of murine embryonic stem cells (ES cells) in the practice of the invention and have failed to disclose use of ES cells from other animals. ES cells having the same capabilities as ES cells from mice are not known to be obtainable from any other animals and to obtain them would require undue experimentation from one of ordinary skill since such cells may not be obtainable. Therefore, claims 1-10 must be limited to mice.

Note that both terms "rodents" and "murine" do not specify mice. "Murine" may be rats and "rodents" include other animals such as hamsters and gerbils.

In addition, claims 5-11 must be limited to the J region or the kappa constant region or the J region and kappa constant region since the specification fails to provide guidance to one of ordinary skill to modify the V region in a similar manner.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim 5 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "substantially intact" is vague and unclear since the metes and bounds of "substantially" are indefinite. In addition, the word "and/or" is vague and unclear since which condition specified in not apparent.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1-6, 8 and 9 rejected under 35 U.S.C. 103 as being unpatentable over Huxley et al taken with Hooper et al and Pachnis et al. Huxley discloses the human HPRT gene on a yeast artificial chromosome is functional when

transferred to mouse L cells by yeast spheroplast fusion (Abstract and page 743, first column). Huxley therefore teaches a method to modify the genome of a mammalian cell using YACs containing a functional copy of a mammalian HPRT gene. Huxley differs from the claims in that the reference fails to disclose modification of the genome of ES cells. However, the secondary references, Hooper and Pachnis, cure the deficiency. Hooper discloses a HPRT deficient mouse embryo (murine ES cells) cell line and further discloses the production of a line of mice bearing the HPRT deficiency. Pachnis discloses that the ability to introduce intact YACs back into cells in culture, or into embryos, would make feasible cellular transformation with large genes or gene complexes as well as the rapid screening of large segments of the mammalian genome to identify genes that complement recessive mutations or confer dominant phenotypes.

Regarding claims 1-3, Pachnis discloses a YAC containing 450 kb of human DNA and that integration was stable.

Regarding claim 3, it would have been obvious to one of ordinary skill to mate the chimeric animals with an animal of the same species to produce offspring carrying the xenogeneic DNA since animal breeding for propagation of particular desirable traits is centuries old.

Regarding claim 4, Huxley discloses (page 742, column 2, top paragraph) that HAT media can be used to select for the active HPRT gene.

Regarding claim 5, Pachnis teaches transfer of human DNA.

Regarding claims 6, 8 and 9, the combination of references renders obvious ES cells containing a modified genome.

Both Huxley and Pachnis provide the motivation to combine the references. Pachnis discloses (page 5113, column 1, last paragraph) "The application of this YAC transfer system to pluripotent embryonic stem cells which are capable of colonizing the somatic as well as the germ cell lineages

when implanted into early mouse embryos, could lead to the generation of transgenic animals that carry and transmit any YAC". In addition, Huxley also provides the motivation to combine the references on page 742, column 2, top paragraph, wherein it is stated "Many HPRT-negative cell lines are available as potential hosts for the HPRT-containing YACs, and HAT media can be used to select for the active HPRT gene". Therefore, both Pachnis and Huxley clearly suggest substituting ES cells for the L cells.

Accordingly, the modification of the method of Huxley by substituting ES cells as suggested by Pachnis and Hooper in order to obtain a method to modify the genome of a recipient murine ES cell was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 7, 10 and 11 are rejected under 35 U.S.C. 103 as being unpatentable over Hooper et al taken with Huxley et al and Pachnis et al. Hooper discloses a HPRT deficient mouse embryo (murine ES cells) cell line and further discloses the production of a line of mice bearing the HPRT deficiency. Hooper differs from the claims in that the reference fails to disclose a transgenic mouse containing a modification of the genome by YACS containing the human HPRT gene However, the secondary references, Huxley and Pachnis, cure the deficiency. Huxley discloses the human HPRT gene on a yeast artificial chromosome is functional when transferred to mouse L cells by yeast spheroplast fusion (Abstract and page 743, first column). Huxley therefore teaches a method to modify the genome of a mammalian cell using YACs containing a functional copy of a mammalian HPRT gene. Pachnis discloses that the ability to introduce intact YACs back into cells in culture, or into embryos, would make feasible cellular

transformation with large genes or gene complexes as well as the rapid screening of large segments of the mammalian genome to identify genes that complement recessive mutations or confer dominant phenotypes.

Both Huxley and Pachnis provide the motivation to combine the references. Pachnis discloses (page 5113, column 1, last paragraph) "The application of this YAC transfer system to pluripotent embryonic stem cells which are capable of colonizing the somatic as well as the germ cell lineages when implanted into early mouse embryos, could lead to the generation of transgenic animals that carry and transmit any YAC". In addition, Huxley also provides the motivation to combine the references on page 742, column 2, top paragraph, wherein it is stated "Many HPRT-negetive cell lines are available as potential hosts for the HPRT-containing YAC, and HAT media can be used to select for the active HPRT gene" and further "The availability of HPRT-negative cells from all tissues of the human and mouse and the existence of HPRT-negative mice are important assets of this system". Therefore, both Pachnis and Huxley clearly suggest the generation of mice having modified genomes.

Accordingly, the modification of the mouse of Hooper by modifying the ES cells with YACs containing the functional human HPRT gene as suggested by Pachnis and Huxley in order to obtain a transgenic mouse having a genome modified by YACs containing a functional copy of the human HPRT gene was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

No claim is allowed.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)308-4227.

An inquiry concerning this communication or earlier communications from the Examiner should be directed to Examiner Suzanne Ziska, Ph.D., at telephone number 703-308-1217. The Examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Elizabeth Weimar, can be reached on (703) 308-0254.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Suzanne Ziska

SUZANNE E. ZISKA
PRIMARY EXAMINER
GROUP 1800
6/22/94